

REMARKS

Upon entry of the foregoing amendment, claims 1-21, and new claims 52-72 are pending in the application. Claims 22-51 are withdrawn by the Examiner under 37 C.F.R. § 1.142(b). Claims 22-51 are canceled without prejudice to, or disclaimer of, the material recited therein. Claims 1-21 stand rejected as not satisfying the enablement requirement under 35 U.S.C. § 112, first paragraph, and as being indefinite under 35 U.S.C. § 112, second paragraph. Also, Claims 1-6, 8-10, 12, and 15-17 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Cooper (U.S. Patent 5,719,055) in view of Meiss et al. (Biotechniques, 2000, 29(3): 476-480).

Claim 1 is amended to describe a vector comprising a nucleic acid sequence encoding: a) a transposase gene operably linked to a first promoter, wherein the nucleic acid sequence 3' to the first promoter comprises the Kozak sequence as set forth in SEQ ID NO: 13, the Kozak sequence being positioned so as to include at least the first codon of the transposase gene; and b) one or more genes of interest operably-linked to one or more additional promoters, wherein the one or more genes of interest and their operably-linked promoters are flanked by transposase insertion sequences recognized by the transposase. The amendment of claim 1 is supported in the specification at page 4, lines 6-19; page 13, line 24 to page 14, line 11; and page 14, lines 13-30 (describing transposase-based vectors with Kozak sequences, and modifications of the first codons of the transposase gene to enhance transposase transcription). Support for the amendment of claim 1 is also found at page 55, line 25 to page 56, line 3, describing construction of the vector of SEQ ID NO:1, and the sequence of SEQ ID NO: 1, with positioning of the Kozak sequence to include the start codon for the transposase, and specifically identifying changes in the wobble positions of the codons for the first 10 amino acids of the transposase protein. Support for the amendment of claims 7 and 11 to include a conalbumin promoter is found at page 17, lines 9-12, page 18, lines 20-28, and page 21, lines 9-14. Support for the amendment of claim 18 is found in the specification, e.g., at page 20, lines 3-11, and page 88, lines 2-3 and 19-23, describing vectors that utilize functional portions of enhancers. Other amendments of the claims are made to improve the syntax of the claims, and/or to correct for changes in antecedent basis or claim dependency due to the amendments. New claims 52-72 include the limitations of

originally filed claims 1, 2, 7, 11, 12-14, 17-21, and thus, are supported by the originally filed claims. Accordingly, no new matter is introduced by the amendment of the claims or the specification.

The specification is amended to clarify that the Kozak sequence ACCATG (SEQ ID NO:13) is positioned 3' (i.e., downstream) of the promoter operably-linked to the transposase. Also, the specification is amended at pages 58, 60, 61, 63, 72, 73, 75, and 76 to describe that for the constructs shown as SEQ ID NO:1 (page 58), SEQ ID NO:2 (page 60), SEQ ID NO:3 (page 61), SEQ ID NO:4 (page 63), SEQ ID NO:29 (page 72), SEQ ID NO:30 (page 73), SEQ ID NO:31 (page 75), and SEQ ID NO:32 (page 76), base pairs 1780-1785 are the Kozak sequence, and base pairs 1783-2987 are the coding sequence for the modified transposase. Support for these amendments of the specification is found in the specification at page 55, line 25 to page 56, line 3, describing construction of the vector of SEQ ID NO:1, with positioning of the Kozak sequence to include the start codon for the transposase, and specifically identifying changes in the wobble positions of the codons for the first 10 amino acids of the transposase protein. Also, support is found in the vectors of SEQ ID NO:1 (page 58), SEQ ID NO:2 (page 60), SEQ ID NO:3 (page 61), SEQ ID NO:4 (page 63), SEQ ID NO:29 (page 72), SEQ ID NO:30 (page 73), SEQ ID NO:31 (page 75), and SEQ ID NO:32 (page 76); the Kozak sequence of SEQ ID NO:13 (ACCATG); and the published sequence for the transposase Tn10 (GenBank accession J01829; referred to at page 57, line 25 of the specification). Thus, an analysis of these sequences shows that the Kozak sequence is included in base pairs 1780-1785 of each of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, and SEQ ID NO:32, and that the modified Tn10 transposase coding sequence begins at base 1783 of each of these sequences (i.e., SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, and SEQ ID NO:32).

Other amendments to the specification add the paragraph claiming priority to related applications under 35 U.S.C. § 119(e) and 120, and remove hyperlink and/or other forms of browser-executable code. Accordingly, no new matter is added by the amendment of the specification.

Interview Summary

An interview was conducted on May 2, 2006. Participating in the interview were the Examiners, Peter Paras and Anoop Singh, inventors Richard Cooper and William Fioretti, and Applicants' representatives, John McDonald and Cynthia Rothschild. Issues discussed were amendments of the claims to overcome the rejection of the claims under 35 § U.S.C. 112, paragraphs 1 and 2, and as being unpatentable under 35 § U.S.C. 103(a) by the references cited in the Office Action mailed on December 27, 2005. It was discussed that Applicants may clarify the position of the Kozak sequence in the vector. Also, the importance of utilizing the Kozak sequence for expression of a prokaryotic transposase in eukaryotic cells was discussed as a non-obvious distinction of Applicants' invention over the cited references. It was also discussed that claim 2 would be revised to clarify the nature of the modification of the first twenty codons of the transposase gene. The Applicants and Applicants' representatives thank the Examiners for participating in the interview and for helping to clarify the outstanding issues in the case.

Election of Claims

The Examiner requested affirmation of the claims elected for prosecution in the application. Office Action pages 2-4. Applicants had provisionally elected claims 1-21 for prosecution in the application in a telephone interview. Applicants respectfully affirm election of claims 1-21 of Group I for prosecution in the application as requested by the Examiner, and cancel the non-elected claims.

Statement of Related Priority Applications

Applicants have amended the specification to include the priority claim as the first line of the specification as requested by the Examiner (Office Action at page 4).

Objections To The Specification

The Examiner objected to the specification as containing embedded hyperlink and/or other form of browser-executable code. Office Action at page 4. Applicants have amended the specification to remove the references to hyperlink as suggested by the

Examiner, and thus, respectfully request that the objections to the specification be withdrawn.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, Is Traversed Or Rendered Moot

The Examiner rejected claims 1-21 as failing to satisfy the enablement requirement. Thus, the Examiner asserted the following:

The specification has exemplified the creation of the vector set forth in SEQ ID NO: 1. However, the specification has not provided guidance correlating to insertion of the Kozak sequence ACCATG in a promoter, such that the Kozak sequence functions to initiate translation. Although the specification asserts that the Kozak sequence in SEQ ID NO: 1 is in the promoter region . . . when the sequence of SEQ ID NO: 1 was examined the Kozak sequence, ACCATG, actually began at base 1780, which is part of the transposase gene coding sequence.

Office Action at pages 5-6.

Applicants have amended the claims to clarify that the Kozak sequence in the vectors of the invention is positioned 3' of the first promoter to enhance expression of the transposase, where the Kozak sequence is positioned so as to include at least the first codon of the transposase gene. Thus, a review of the vector sequences described in the specification indicates that for several of the vectors described in the specification, the Kozak sequence ACCATG (SEQ ID NO:13) is positioned 3' (i.e., downstream) of the promoter operably-linked to the transposase, e.g., at base pairs 1780-1785 of the vectors, with the transposase start codon (ATG) positioned at base pair 1783. Thus, Applicants respectfully assert that as amended, the claims are enabled for the use of a Kozak sequence as part of the vector to promote translation of the transposase gene, and request that the rejection be withdrawn.

The Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph, Is Traversed Or Rendered Moot

The Examiner rejected claims 1-21 as being indefinite under 35 U.S.C. § 112, second paragraph, for use of the term "modified" Kozak sequence, and for claiming a Kozak sequence as part of a promoter. Thus, the Examiner stated

[I]t is not clear if the modified sequence is ACCATG or a sequence comprising ACCATG. . . . [S]ince Kozak sequences (all combinations, including ACCAUG) are naturally occurring and found in mRNAs, it is unclear how a Kozak sequence can be modified.

...

Claim 1 . . . requires that the Kozak sequence is only located somewhere in a promoter. For a Kozak sequence to be functional, it needs to be operably linked [to] a coding sequence. If a Kozak sequence is located elsewhere, for example in a non-transcribed promoter region, it will not function as a Kozak sequence and promote initiation of translation.

Office Action at page 7-8.

Applicants have amended claim 1 to remove the term “modified” from the description of the Kozak sequence, as the term “modified” is not required to describe the Kozak sequences used in the claimed constructs of the invention. Also, claim 1 is amended to describe that the Kozak sequence in the transposon-based vector is not part of the first promoter, but is 3’ of the first promoter, and positioned so as to encode for at least the first codon of the transposase gene. Applicants therefore respectfully assert that as amended, claim 1 is not indefinite under 35 U.S.C. § 112, second paragraph.

The Examiner also stated that claim 2 was indefinite in reciting one to twenty codons at “a beginning” of the transposase gene, in that the claim reads on a transposase gene having more than one beginning. Office action at page 21. Applicants have amended claim 2 to describe that at least “one of the first twenty codons of the transposase gene” are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without modifying the amino acid encoded by the codon. Applicants respectfully assert that as amended, claim 2 is not indefinite under 35 U.S.C. § 112, second paragraph.

Thus, Applicants respectfully assert that as amended, claims 1-21 are not indefinite under 35 U.S.C. § 112, second paragraph, and request that the rejection be withdrawn.

***The Rejection of Claims 1-6, 8-10, 12, and 15-17 Under 35 U.S.C. § 103(a) Is
Traversed Or Rendered Moot***

The Examiner rejected claims 1-6, 8-10, 12 and 15-17 as being unpatentable over Cooper R., U.S. Patent No. 5,719,055 (hereinafter "Cooper") taken with Meiss (Biotechniques, 2000, 29(3): 476-480 (hereinafter "Meiss"). Thus, the Examiner stated:

Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. . . . For example, Meiss et al. taught a vector for providing expression of a gene of interest in either prokaryotic or vertebrate cells. The vector comprised a CMV promoter in operable linkage with a Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag.

Office Action at pages 9-11.

Applicants respectfully assert that the claimed invention is not rendered prima facie obvious by the cited references. The vectors of the present invention provide constructs that allow for improved expression of the transposase protein, thereby resulting in a significant increase in insertion frequencies. Applicants note that the vectors of the invention are far more efficient than vectors used in the prior art. Thus, as noted in the specification at page 13, lines 15-23, the vectors of the present invention produce integration frequencies an order of magnitude greater than other vectors commonly used at the time of the invention.

Applicants respectfully assert that neither of the cited references teach or suggest a vector that uses a Kozak sequence to allow for a prokaryotic gene to be expressed and function in a eukaryotic cell in vivo. Meiss is concerned with a vector that may be used in vitro, to allow for expression of eukaryotic proteins to be harvested from the in vitro culture. In contrast to Applicants, Meiss teaches using both a prokaryotic and a eukaryotic translation initiation sequences upstream of a eukaryotic of interest to allow for expression of a eukaryotic gene (e.g., DFF40 or EGFP) in either a prokaryotic cell or

a eukaryotic cell. Thus, Meiss does not describe or suggest use of a Kozak sequence for expression of a transposase protein (which may either be prokaryotic or eukaryotic in origin), but is concerned with expression of eukaryotic proteins either in prokaryotic cells or eukaryotic cells. In contrast, Applicants' vector is optimized to allow expression of a prokaryotic protein in eukaryotic cells. Applicants' vectors allow not only for expression of a prokaryotic transposase protein in a eukaryotic cell, but proper function, in vivo, of the prokaryotic transposase in eukaryotic cells for the purpose of stable gene incorporation into a recipient genome.

Also, as noted by the Examiner, the vectors of Cooper did not employ a Kozak sequence as part of the sequence upstream of the transposase. Instead, Cooper teaches that a transposase-based vector comprising a gene of interest may be designed without the use of a Kozak sequence to promote translation of a transposase gene (either eukaryotic or prokaryotic) in eukaryotic cells. Thus, one of skill in the art reading Cooper would not be motivated to incorporate a Kozak sequence in a transposon-based vector, as this sequence was not required for transformation of mammalian and/or fish cells as described in Cooper.

Applicants respectfully assert that, without the hindsight gained by the disclosure of the instant application, the references of Meiss and Cooper do not describe, teach or suggest to include a Kozak sequence as a means to improve transposase-mediated integration of a gene of interest into a eukaryotic genome.

Thus, Applicants respectfully assert that as amended, the claimed invention is patentable under 35 U.S.C. § 103(a) over Cooper in view of Meiss, and respectfully request that the rejection be withdrawn.

Allowable Subject Matter

The Examiner stated that claims 7, 11, 13, 14 and 18-21 appeared to be free of the art. Applicants have added new claims 52-66 that incorporate the limitations of the allowable subject matter into amended claim 1. Claim 52 incorporates the limitations of original claims 7 and 11 into claim 1, and new claim 60 incorporates the limitations of original claim 14 into amended claim 1. Based on the amendments made to the claims, and the arguments presented herein, Applicants respectfully assert that these new claims are in a form for immediate allowance.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

Date: May 30, 2006


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